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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SODERQUIST, ARLEN	

ART UNIT	PAPER NUMBER
1797	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,043	SALOMA ET AL.	
	Examiner	Art Unit	
	Arlen Soderquist	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8-26-05*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

2. Claims 1-4, 7 and 18 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Iketaki (US 6,667,830). In the patent Iketaki teaches a microscope system comprising an adjusted specimen and a microscope body, wherein the adjusted specimen is dyed with molecule which has three electronic states including at least a ground state and in which an excited wavelength band from the first electron excited state to the second electron excited state overlaps a fluorescent wavelength band upon deexcitation through a fluorescence process from the first electron excited state to a vibrational level in the ground state. There is provided a novel microscope system which is enabled to condense an erase light for exciting a molecule in the first electron excited state to the second electron excited state in an excellent beam profile by using a simple, compact optical system and which has high stability and operability and an excellent super-resolution. Figure 26 and example 4 teach a system in which two different wavelengths of light are produce from a single source through the use of a Raman shifter (4). The resulting two wavelengths are used for fluorescent excitation of the dye on a sample (100) that is moved by a stage (10).

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 1, 7, 18-22 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mandella (US 6,369,928) in view of Alfano (US 6,208,886). In the patent Mandella teaches a fiber-coupled, angled-dual-illumination-axis confocal scanning microscopes integrated into a scanning head and a vertical scanning unit for performing reflective and two-photon fluorescence imaging. The angled-dual-illumination-axis confocal scanning head is configured such that two illumination beams intersect optimally at an angle .theta. within an object and the scanning is achieved by pivoting the illumination beams and their corresponding observation beams using a single scanning element, thereby producing an arc-line scan. The vertical scanning unit causes the angled-dual-illumination-axis confocal scanning head to move towards or away from the object, thereby yielding a vertical cross-section scan of the object. The angled-dual-illumination-axis confocal scanning microscope have advantages of enhanced resolution, faster scanning, higher sensitivity and larger dynamic range of detection, a larger field of view and a longer working distance, and a compact and integrated construction. Column 2, lines 39-67 teach that two-photon fluorescence microscopy requires simultaneous absorption of two photons from any combination of wavelengths, so long as the net energy requirements for exciting the particular types of fluorophores being used are satisfied. An inherent advantage of two-photon fluorescence is that the two-photon absorption occurs only within a confined region where the two incident beams overlap, hence eliminating unwanted, spurious fluorescence and scattered light. Moreover, because two-photon excitation depends on the square of the excitation power, the excited volume is restricted to the focal point, providing an equivalent of confocal conditions. Additional advantages provided by two-photon (and multi-photon) excitation include longer

penetration depth within a specimen (since longer wavelengths are employed, thus reducing scattering losses), reduced photobleaching and phototoxicity, and reduced background noise. Accordingly, two-photon excitation has been of considerable interest for microscopy, fluorescence spectroscopy, and for single-molecule detection. For instance, two-photon fluorescence microscopy has been used in the art for imaging various types of fluorophores (or fluorophore indicators attached to proteins and biological cells) that are of particular interest to biomedical applications. It has also been used as an alternative way of attaining enhanced resolution and greater flexibility in imaging. Column 6, lines 22-28 teach that the scanning means can include many types of scanning mechanisms including mechanical scanning mechanisms. Column 8, lines 32-42 teach that for the two-color two-photon (2C2P) fluorescence image information , the first and second illumination beams should each provide light with only one of the two required wavelengths, such that 2C2P excitation light is provided only in the region where the two illumination beams overlap both spatially and temporally. Column 9, lines 27-34 teach that the light sources can be a variety of things including a pulsed laser and the detector can be a variety of things including a photodiode or a photomultiplier tube. Figure 2A shows the device (200) including the confocal scanning head (201) and the movable carriage (202). Figure 2A also shows the detector coupled to the scanning head through an optical fiber (165). The sentence bridging columns 18-19 teach that the movable carriage can be driven by a variety of means including a motor or other types of actuator means. Column 24, lines 46-67 teach that the two illumination beams can be derived from a single light source by means of a frequency doubler (607) as shown in figure 6. Mandella does not teach a three axis scanning stage.

In the patent Alfano teaches an apparatus utilizing non-linear optical signals for use in constructing a three-dimensional tomographic map of an in vivo biological tissue for medical disease detection purposes. In one embodiment, said apparatus comprises a stage for supporting the in vivo biological tissue; a laser for illuminating the in vivo biological tissue with a focused beam of laser light, the light emerging from the in vivo biological tissue comprising fundamental light, harmonic wave light, and fluorescence due to multi-photon excitation; a filter for selectively passing only at least one of the harmonic wave light and the fluorescence; one or more detectors for individually detecting each of the harmonic wave light and the fluorescence

selectively passed; and a mechanism for moving the laser relative to the stage in x, y and z directions. Column 4, lines 50-65 give a description of the mechanism for moving the laser relative to the stage in the x, y and z directions.

It would have been obvious to one of ordinary sill in the art at the time the invention was made to replace the movement mechanism of Mandella with the movement mechanism of Alfano because of their use in an equivalent setting.

5. Claims 2-6, 10-15 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mandella in view of Alfano as applied to claims 1 and 22 above, and further in view of Bickel. Mandella does not teach using a Raman shifter to produce the appropriate wavelengths for use in the device.

In the paper Bickel teaches two-photon spectra of glyoxal. The two-photon excitation spectrum of the $^1A_u(S_1)$–$^1A_g(S_0)$ transition in trans-glyoxal is observed in the region of 21 800–25 400 cm^{-1}. The excitation source is the H_2 Raman shifted output of a pulsed dye laser. The source yields tunable output from 0.7 to 1.4 μm and enables both one- and two-color two-photon spectra to be observed. These spectra are complementary to the well known one-photon spectra for this transition. However, the two-photon selection rules cause much of the vibrational structure to be simplified. Many of the observed bands belong to the torsional mode, 7, revealing vibrational quanta up to 12 in the excited state and 8 in the ground state. The two-photon rotational contours for a number of transitions are calculated for comparison with the observed spectra. The paragraph bridging pages 1752-1753 teaches that the two color situation was obtained from the Raman shifter cell by allowing two different wavelengths to pass out of the cell. Table 1 shows the various combinations used.

It would have been obvious to one of ordinary sill in the art at the time the invention was made to use the pumped Raman shifter of Bickel as the single source of Mandella because of the recognized ability to produce excitation light of multiple wavelengths for use in a two color fluorescence measurement situation.

6. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mandella in view of Alfano as applied to claim 1 above, and further in view of Kask. Mandella does not teach the multiphoton excitement used for Raman scattering.

In paragraph [0032] of the patent Kask teaches that multiple photon excitation in which the sum, difference or any combination of wave frequencies of two, three or more photons is used for excitation of the secondary emission of the sample which can be e.g. luminescence (fluorescence) or second order Raman scattering. Such an excitation scheme has an advantage in the sense that the excitation probability is not linearly dependent on excitation intensity, but on the second or higher power. Thus, the multiple photon excitation is mostly limited to the volume of the laser focus, whereas outside the laser focus no spurious excitation is generated. Appropriate laser sources of picosecond or subpicosecond pulses are well known to those of skill in the art.

It would have been obvious to one of ordinary sill in the art at the time the invention was made to use the method of Mandella for Raman scattering as taught by Kask because of the advantages as taught by Mandella and Kask.

7. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mandella in view of Alfano as applied to claim 1 above, and further in view of Kask. Mandella does not teach measuring a refractive index change.

In the paper Franko teaches the development of a double-beam, dual-wavelength thermal-lens spectrometer for simultaneous measurement of absorption at two different wavelengths. The dual-wavelength pump/probe configuration thermal lens spectrometer is capable of simultaneously measuring a change in refractive index from the thermal lens at two different wavelengths. In this instrument, the two excitation beams were derived from the same argon ion laser, which operated in a multiline mode. The sample was excited by these two wavelengths alternatively and the corresponding thermal lens signals were monitored by a He-Ne probe laser. Compared to the single-wavelength techniques, the advantages of this dual-wavelength apparatus include its ability to correct for the solvent background absorption and its improved selectivity. The solvent background absorption was alleviated because this technique measures the difference between the two thermal lens signals at the two excitation wavelengths. The ratio of the two signals provides fingerprints and identification of the analyte. Furthermore, it enables the determination of trace chemical species in the presence of interference species at much higher concentrations.

It would have been obvious to one of ordinary sill in the art at the time the invention was made to use the method of Mandella for measuring a refractive index change as taught by Franko because of the advantages as taught by Franko.

8. Claims 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mandella in view of Alfano and Bickel as applied to claim 13 above, and further in view of Kenny (US 5,491,344) or Merriam (US 6,958,854). Mandella does not teach methane or deuterium gases in a Raman shifter.

In the abstract of the patent Kenny teaches a method and system for examining the composition of a fluid or solid sample using fluorescence and/or absorption spectroscopy. In one embodiment, the system is adapted for use in examining liquid effluents as they elute from the end of a liquid chromatography column and comprises a Nd:YAG laser coupled to a harmonic generator. Pulses of the fourth harmonic therefrom are focused into a Raman shifter filled with a mixture of hydrogen and methane gases. The laser pulses have an intensity sufficient to produce an array of different-colored laser pulses by stimulated Raman scattering within the Raman shifter. These different-colored pulses are then dispersed according to their respective wavelengths and then launched into a plurality of optical fibers. The fibers transmit the different-colored pulses to a specially-designed detection cell, where they simultaneously excite a flowing fluid sample contained within the cell at the same point of axial fluid flow.

In the patent Merriam teaches Raman shifters using gases. Column 1, lines 58-62 teach that Raman shifting was the first nonlinear effect discovered after the invention of the laser in 1960, and as such, there is a great body of research on the subject. Common Raman gasses are molecular hydrogen (H_2) and deuterium (D_2). The number of these sidebands and their relative intensities depend upon the particular parameters of the apparatus.

It would have been obvious to one of ordinary sill in the art at the time the invention was made to use the notoriously well known Raman shifting gases of deuterium or methane as taught by Merriam or Kenny in the method of Mandella because of their known uses to produce a plurality of frequencies for excitation spectroscopy as taught by Merriam and Kenny.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The additionally cited art relates to various Raman shifters and multiphoton excitation apparatus and methods.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arlen Soderquist whose telephone number is (571)272-1265. The examiner can normally be reached on Monday-Thursday and Alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Vickie Kim can be reached on (571) 272-0579. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Arlen Soderquist/
Primary Examiner, Art Unit 1797